Remarks

Status of the Claims and Support for the Amendments

Upon entry of the foregoing amendment, claims 1, 3-7, 9-21, 23, 24, 35, 38, 59, 61-63, 65, 67, 73-77, 79, 90, 94, 109-131, 134, 137, and 140-171 are pending in the application, with claim 1 as the sole independent claim. Claims 1, 3-7, 9-21, 23. 24, 59, 61-63, 65, 67, 73-77, 109, 111-117, 119-126, 130, 134, 137, 140-143, 146-157, and 160-171 have been amended.

The amended claims are fully supported in the specification and original claims. In particular, regarding the amendment of claims 1, 142, and 143 to recite a percentage purity, the specification clearly supports a composition comprising a conjugate that is 95% or more pure, 98% or more pure, or 99% or more pure, *e.g.*, in paragraphs [0053], [0112], [0114], [0117], [0070] and [0075]; *see also*, Examples 5 and 6 and the discussion below regarding the rejection under 35 U.S.C. § 112, first paragraph. The claims were also amended to correct clerical errors.

Therefore, the claims are fully supported by the specification. Accordingly, no new matter has been added by this amendment.

The Information Disclosure Statements: Concise Statements of Relevance

The Examiner asserted that concise statements of the relevance of particular foreign patent documents have not been provided. Applicants respectfully traverse and point out that such statements have been provided. Specifically, such statements were provided as follows:

- For JP 2002-527491: See page 1 of the Thirteenth Supplemental Information Disclosure Statement filed April 15, 2010, listed in PAIR as 04-

15-2010 TRAN.LET Transmittal Letter ("13th Suppl. IDS"); and page 1 of the Fourteenth Supplemental Information Disclosure Statement filed March 4, 2011, listed in PAIR as 03-04-2011 TRAN.LET Transmittal Letter ("14th Suppl. IDS");

- For JP 50-42087: See pages 1-2 of the 13th Suppl. IDS; and pages 1-2 of the 14th Suppl. IDS;
- For JP 53-24033: See page 2 of the 13th Suppl. IDS; and page 2 of the 14th Suppl. IDS;
- For JP 8-283282: See page 2 of the 14th Suppl. IDS; and
- For JP 6-507410: See page 2 of the 14th Suppl. IDS.

For the Examiner's convenience, Applicants reproduce below the concise statements of relevance that were included in the 14th Suppl. IDS.

Document FP17 (JP 2002-527491 A) is a foreign language document. Based on information and belief, document FP17 is a translation of WO 00/23114 A2, which is of record in the present application as document FP12. It is submitted that the English language document FP12 satisfies the requirement for a concise explanation of relevance for document FP17. M.P.E.P. 609.04(a)III.

Document FP18 (JP 50-42087) is a foreign language document. An English language patent (U.S. Patent No. 4,179,337) in the same patent family as document FP18 is of record in the present application as document AE1. Based on U.S. Patent No. 4,179,337, document FP18 appears to relate to certain polypeptides that are coupled to polyethylene glycol or polypropylene glycol having a molecular weight of 500 to 20,000 daltons.

Document FP19 (JP 53-24033) is a foreign language document. An English language patent (U.S. Patent No. 4,261,973) in the same patent family as document FP19 is of record in the present application as document US11. Based on U.S. patent No. 4,261,973, document FP19 appears to relate to allergen-containing substances that are covalent conjugates of the allergen molecules with water-soluble polymers.

Document FP20 (JP 08-283282 A) is a foreign language document. An English language document (WO 87/06838) is listed as document FP22. Based on WO 87/06838, document FP20 appears to relate to certain immunogenic conjugates.

> Document FP21 (JP6-507410 (T)) is a foreign language document. Based on information and belief, document FP21 is a translation of WO 92/19273 A1, which is listed as document FP23. It is submitted that the English language document FP23 satisfies the requirement for a concise explanation of relevance for document FP21. M.P.E.P. 609.04(a)III.

Therefore, consideration of these documents by the Examiner and a notation of same on the record are respectfully requested.

Rejections under 35 U.S.C. § 112, First Paragraph: Written Description

Claims 1, 3-7, 9-21, 23, 24, 35, 38, 59, 61-63, 65, 67, 73-77, 79, 90, 94, 109-131, 134, 137, and 140-171 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Office Action at pp. 3-6. The Examiner's position appears to be that the phrase "at least 95% of said polyalkylene glycol(s) is or are attached to said peptide, protein or glycoprotein at a single site on said polyalkylene glycol(s), wherein a hydroxyl group is present on at least 95% of the distal polyalkylene glycol termini in said conjugate" constitutes new matter. *Id.* at p. 4. Applicants respectfully traverse the rejection as applied to the pending claims.

The pending claims are fully supported in the specification. The claims have been amended and no longer recite the phrase to which the Examiner objected. Claim 1 now recites:

> A composition comprising a conjugate 95% or more pure, said conjugate comprising a peptide, protein or glycoprotein covalently attached to at least one linear or branched polyalkylene glycol(s),
>
> wherein said linear or branched polyalkylene glycol(s) is or are attached to said peptide, protein or glycoprotein at a single site on said linear or branched polyalkylene glycol(s),
>
> wherein a hydroxyl group is present on all of the distal polyalkylene glycol termini in said pure conjugate, and

> wherein said pure conjugate exhibits reduced antigenicity compared to a second conjugate comprising the same peptide, protein or glycoprotein linked at the same site or sites on the peptide, protein or glycoprotein to the same number of polyalkylene glycol(s) of the same size and the same linear or branched structure, wherein an alkoxyl or an aryloxyl group is present on the distal polyalkylene glycol termini in said second conjugate.

Thus, claim 1 now recites a "composition comprising a conjugate 95% or more pure." The remaining claims depend from claim 1. In addition, claims 142 and 143 were amended to recite a composition comprising a conjugate "98% or more pure" and "99% or more pure," respectively. These three limitations are supported, e.g., as follows:

> Purified: As used herein, when the term "purified" is used in reference to a molecule, it means that **the concentration of the molecule being purified has been increased relative to molecules associated with it in** its natural environment, or **the environment in which it was produced, found or synthesized.** Naturally associated molecules include proteins, nucleic acids, lipids and sugars, but generally do not include water, buffers, and reagents added to maintain the integrity or facilitate the purification of the molecule being purified. For example, even if a given protein in a crude extract is diluted with an aqueous solvent during column chromatography, protein molecules are considered to be purified by this chromatography if naturally associated nucleic acids, non-desired proteins and other biological molecules are separated from the subject protein molecules. According to this definition, **a substance may be** 5% or more, 10% or more, 20% or more, 30% or more, 40% or more, 50% or more, 60% or more, 70% or more, 80% or more, 90% or more, **95% or more, 98% or more, 99% or more, or 100% pure** when considered relative to its contaminants.

Original specification and 2004/0062746, para. [0053] (emphasis added). The specification provides further support as follows:

> **Purification of the polymer-coupled bioactive component** can be effected by means commonly employed by those skilled in the art, such as, for example, size-exclusion chromatography, ion-exchange chromatography, ultrafiltration, dialysis, and the like. Solutions of the

> reaction product can, if desired, be concentrated with a rotary evaporator and the product can be obtained in the dry state by lyophilization.

Original specification, para. [0091] (para. [0112] in 2004/0062746) (emphasis added). In addition, the specification states:

> The bioactive component can be reacted with the monofunctionally activated branched poly(ethylene glycol) polymers discussed above (particularly one or more monofunctionally activated, branched dihydroxyPEGs, *e.g.*, dihydroxyPEG-lysine) in an aqueous reaction medium that can be buffered, depending on the pH requirements of the nucleophile and the activated polymer. The optimal pH for the reaction is generally between about 6.5 and about 8.5 and preferably about 7.4 for maintaining the solubility and stability of most polypeptides. The optimal pH for coupling an activated PAG, *e.g.*, NPC-PEG, to a mammalian uricase is approximately pH 10, while the optimal pH for selectively coupling certain activated PAGs to the *N*-terminal *alpha* amino group of a protein or peptide is in the range of about 4 to about 7. The optimal reaction conditions necessary to maintain the stability of the bioactive component, the reaction efficiency, *etc.*, are within the level of ordinary skill in the art. The preferred temperature range is between about 4°C and about 40°C. The reaction temperature must not exceed the temperature at which the nucleophile may denature or decompose. It is preferred that the nucleophile be reacted with an excess of the activated branched polymer. **Following the reaction, the conjugate is** recovered and **purified**, for example, by diafiltration, column chromatography, combinations thereof, or the like.

Original specification, para. [0093] (para. [0114] in 2004/0062746 (bold emphasis added). The specification also states:

> **Following the coupling reaction, conjugates** that are derivatized to various extents **can be separated** from each other using size-exclusion and/or ion-exchange chromatography, as described by Sherman, M.R., *et al.* (1997) *supra*. For example, chromatography on a Superdex® 75 brand HR 10/30 column or a Superdex® 200 brand HR 10/30 column (Amersham Pharmacia Biotech, Piscataway, NJ) permits the separation of protein molecules that are PEGylated to different extents, as well as their separation **from residual free PEG and from most byproducts of the**

> **coupling reaction** (*see* commonly owned, co-pending U.S. Patent Application No. 10/183,607, *supra*).

Original specification, para. [0096] (para. [0117] in 2004/0062746) (bold emphasis added). Therefore, the amended claims are explicitly supported.

Further support for compositions comprising conjugates that are 95%, 98%, or 99% or more pure is found the following passages, which describe methods that produce such compositions.

> In an alternative aspect of the present invention, **monofunctionally activated PEGs can be synthesized by controlling the extent of activation** of linear PEGs containing hydroxyl groups at both ends ("PEG diols") **in order to limit the amount of *bis*-activated PEG to an acceptably low level, *e.g.*, <5%, preferably <2% or more preferably <1%,** as an alternative to the method shown in Example 5. In a particularly preferred aspect, monofunctionally activated PEGs can be synthesized from monofunctional PEGs from which an unreactive blocking group can be removed following the derivatization of the PEG, without removing the derivatizing group. An example of a derivatized PEG is a PEG-carboxylic acid and examples of unreactive blocking groups that can be removed following derivatization are aryloxyl groups (Bentley, M.D., *et al.*, PCT publication WO 01/26692 A1), trityl groups (Kocienski, P.J., (1994) *Protecting Groups*, Georg Thieme Verlag, Stuttgart, pp. 54-58), and *t*-butoxyl groups. The *t*-butoxyPEG-carboxylic acid can be activated, *e.g.*, with *N*-hydroxysuccinimide. Finally, the *t*-butoxyl group can be removed by anhydrous acidolysis to produce an activated PEG carboxylic acid derivative that has a hydroxyl group, instead of a methoxyl group at the distal end of the polymer. In a more preferred embodiment, the *t*-butoxyPEG-carboxylic acid can be converted to hydroxyPEG-carboxylic acid by acidolysis prior to activation of the carboxyl group with *N*-hydroxysuccinimide. In another embodiment of this invention, *t*-butoxyPEG-acetals are synthesized by contacting *t*-butoxyPEG with a haloacetal and converting the product to a hydroxyPEG-acetal or hydroxyPEG-aldehyde by selective anhydrous acidolysis to remove the *t*-butoxyl group. The acetal may be converted to an aldehyde (or an aldehyde hydrate) in preparation for its coupling to an amine-containing compound by reductive alkylation (Bentley, M.D., *et al.*, U.S. Pat. No. 5,990,237). In another embodiment, an aryloxyl protecting group that is distal from the reactive terminus of the polymer can be removed by catalytic hydrogenolysis, thereby producing a

monoactivated hydroxyPAG of this invention. Alternatively, reversible blocking of all except one of the terminal hydroxyl groups, as described in Example 6, can be employed in the synthesis of monofunctionally activated hydroxyPAGs.

* * * *

In certain embodiments of the invention, **it is desirable to minimize the formation of intramolecular and intermolecular cross-links by polymers such as PEG during the reaction in which the polymer is coupled to the bioactive component to produce the conjugates of the invention. This can be accomplished by using polymers that are activated at only one end** (referred to herein as "monofunctionally activated PEGs" or "monofunctionally activated PAGs") **or polymer preparations in which the percentage of bifunctionally activated polymers** (referred to in the case of linear PEGs as "*bis*-activated PEG diols") **is** less than 30%, or more preferably less than 10% or **most preferably less than 2%** (w/w). The use of activated polymers that are predominantly monofunctional can minimize the formation of all of the following: intramolecular cross links within an individual protein molecule, "dumbbell" structures, in which one strand of polymer connects two protein molecules, and larger aggregates or gels. When activated polymers that react with amino groups are used, the theoretical maximum number of strands of polymer that can be attached to one molecule of protein corresponds to the total number of amino groups. The actual number of amino groups that are accessible on the surface of a protein under any particular conditions of polymer coupling may be smaller than the theoretical maximum.

Original specification, paras. [0062] and [0067] (paras. [0070] and [0075] in 2004/0062746) (bold emphasis added); *see also*, Examples 5 and 6. Such language provides further support for the amended claims.

Therefore, the claims are fully supported by the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Conclusion

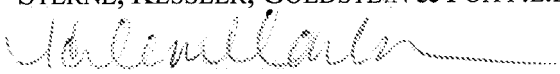
All of the stated grounds of rejection have been properly traversed. Applicants therefore respectfully request that the presently outstanding rejections be reconsidered and withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply are respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Helene C. Carlson
Attorney for Applicants
Registration No. 47,473

Date: July 27, 2011

1100 York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

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